Potential Polymorphs of Aspirin

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ABSTRACT: Aspirin is only found experimentally in one crystal structure. In this article, the method of Karfunkel and Gdanitz is used to predict potential polymorphs of aspirin. The known structure, containing a nonplanar conformer is found, along with a number of other low energy structures, many of which are based on a planar conformer. Semiempirical and *ab initio* calculations show that the planar conformer is less stable than the experimentally known one. Force field calculations suggest that the planar conformer is more stable. The lattice energy of the experimentally known crystal structure is 1.4 kcal/mol lower than any of the potential crystal structures, even though there are a number of structures with lower total (lattice + intramolecular) energies. Conformational maps indicate that another stable conformation occurs within a few kilocalories per mole of the known structure. Polymorphs are predicted for this conformer, but it is found to pack poorly. It is proposed that routes to producing polymorphs of aspirin might be found if consideration is given to promoting the stability of the planar conformer with appropriate solvents or additives. © 1999 John Wiley & Sons, Inc. J Comput Chem 20: 262–273, 1999

Keywords: polymorphism; polymorph prediction; aspirin; conformational flexibility; crystallization

Introduction

Aspirin [acetylsalicylic acid or 2-(acetyloxy)-benzoic acid] is a well-known molecule with a number of pharmaceutical applications.[1] Although it was first synthesized in 1897, and has subsequently been the subject of numerous scientific studies, it is generally thought to exist in only one crystalline form. Evidence that more than one form might be isolated was generated between 1967 and 1973. This was based on observations of crystal habit from different solvents,[2] melting point differences,[3] dissolution studies[4–8] and measurements of pKa.[9] There followed a number of letters to journals pointing out that these observations contained insufficient physical data to prove unequivocally the existence of more than one poly-

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morphic form.[10–12] Unfortunately, no x-ray diffraction data were given by the investigators for the new forms. Two phenomena constitute possible sources of the differences noted between various batches of aspirin: the influence of different solvents on crystal habit,[13] and differing rates of degradation (in particular, hydrolysis).[14] The intriguing history of this important molecule is one of the reasons it was chosen for this study on polymorph prediction.

The known crystal structure of aspirin was first solved by Wheatley[15] and subsequently confirmed with greater accuracy by Kim et al.[16] The latter solution can be obtained from the Cambridge Crystallographic Database[17] as ''refcode'' ACSALA01. The crystal structure is based on centrosymmetric carboxylic acid dimers, as shown in Figure 1. Such dimers are typical of molecules with a carboxylic acid group.[18] Aspirin has three bonds about which rotation is possible, as shown in Figure 2. Thus, it provides a model upon which ideas concerning the investigation of conformational flexibility and polymorphism can be developed.

In this article, the results of solid state structure prediction on aspirin are reported. The methodology used is centered on the program C^2 POLYMORPH[19] as employed previously in an investigation of potential packing arrangements for acetic acid.[20] The review of methods of crystal structure prediction, provided in the introduction to that article is still valid, and will not therefore be reproduced here. However, one study is worth specific mention—that of Gavezzotti and Filippini, who predicted crystal structures of aspirin based on preconstructed dimers.[21] Their work suggested that a structure other than the known crystal structure might be experimentally realizable.

The previous work of ref. 20 was successful in that the known crystal structures of acetic acid and one known structure of each of its halogenated analogs were among the structures predicted. In addition, a structure was found for acetic acid that gave an x-ray powder pattern similar to that of a low temperature, high pressure phase, thus offering a potential structure solution to that data. However, it was found that the force field, DREIDING 2.21,[22] used to describe molecular interactions, was inaccurate in its description of carboxylic acid group hydrogen bonds and halogen–halogen interactions. As a consequence, it was not possible to be confident in the energy ranking of predicted structures: a significant number of potential structures being located closer to the global energy minimum than known structures in all cases. No significantly improved force field has become available for use within C^2 POLYMORPH subse-

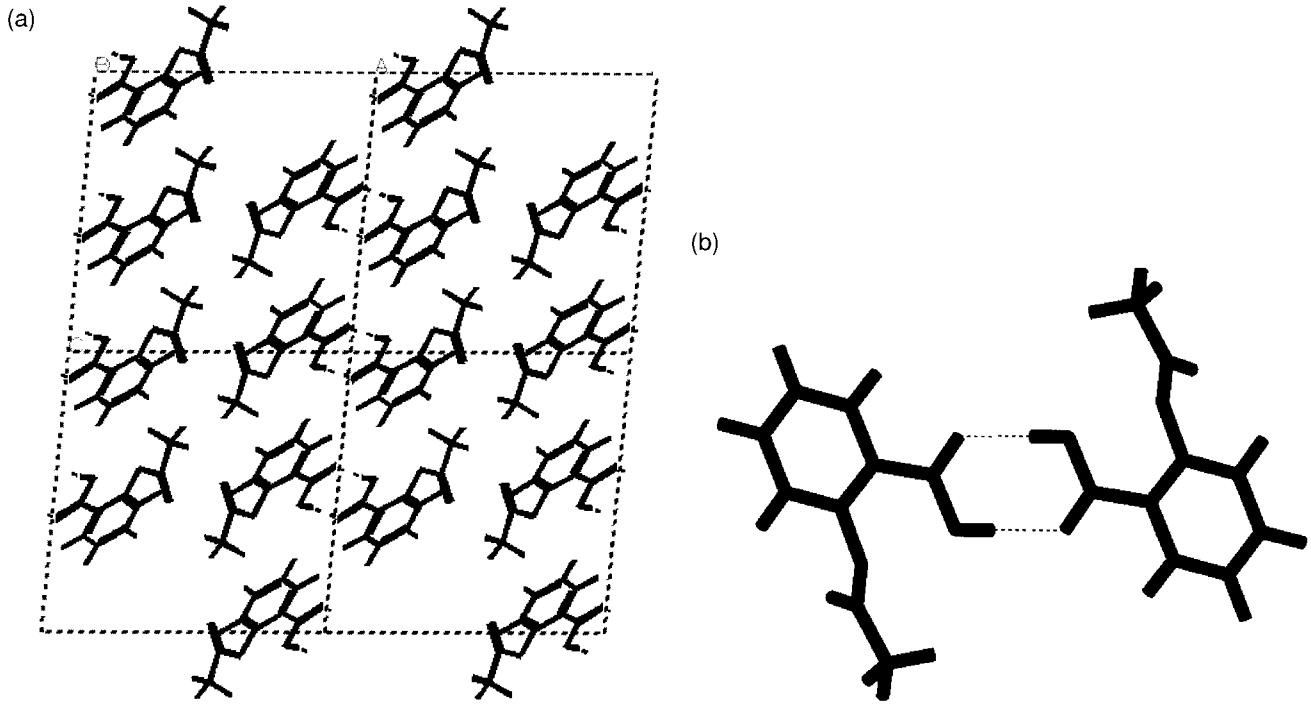

FIGURE 1. (a) The known crystal structure of aspirin. (b) A dimer from the crystal structure.

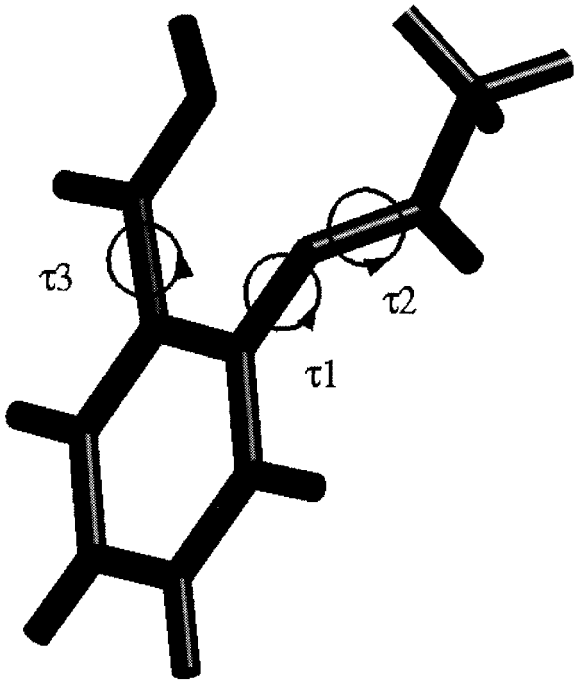

FIGURE 2. Bonds about which rotation of consequence for crystal packing may occur in the aspirin molecule.

quently and, as a consequence, DREIDING 2.21 was also used in this study. The aforementioned limitations will be taken into account and other properties of this force field, which became evident through its application to aspirin, will be discussed later in this text.

Computational Methodology

QUANTUM CHEMISTRY CALCULATIONS

The key to successful structure prediction is said to be the generation of an optimized molecular conformation and atomic point charges that are a fit to the electrostatic potential (ESP) of an *ab initio* calculation. This requirement was investigated in some detail in the previous work.[20] It was not found to offer a significant improvement in predictive capability over work performed with the crystal structure conformer, but this regime is followed in this study. The crystal structure (CS) molecular conformer (CSC) was extracted from ACSALA01 and optimized at the 6-31G** level, using the restricted Hartree–Fock (RHF) formalism. Atomic charges were generated using the method of Merz, Singh, and Kollman (MSK).[23] These calculations were performed using the program Gaussian-92.[24]

CONFORMATIONAL MAPPING

The conformation of aspirin was investigated to determine whether there were any low energy conformers other than that observed in the CS. A series of investigations on other molecules has indicated that CS conformers are not necessarily the lowest energy conformers.[25] This observation leads to the thesis, first touched on by Etter et al,[26] that it may be possible to identify unknown low energy conformers by molecular modeling, predict CSs for them, and hence postulate experimental conditions under which they might be prepared. If this thesis is correct, a practical demonstration of it would represent a breakthrough in the field of crystal engineering.[27]

Ignoring rotation of the methyl groups, aspirin has three dihedral angles that could vary. These are denoted τ_1, τ_2, and τ_3 as shown in Figure 2. However, only τ_1 and τ_2 need to be considered because the carboxylic acid group is usually in the same plane as the phenyl ring and only when halogens are in the ortho position does any significant deviation from planarity occur.[18] Conformational maps of these torsions (τ_1 and τ_2) were calculated in two ways:

1. Using the AM1 semiempirical quantum mechanics methods in MOPAC-93.[28]
2. Using the DREIDING 2.21 force field with electrostatics calculated from 6-31G** ESP charges.

STRUCTURE PREDICTION

The generation of energetically feasible CSs for a particular molecule tests our ability to solve the problem of locating the global energy minimum, and other low energy local minima. Generally, it is thought that polymorphs that are experimentally realizable have structures within ca. 1 kcal/mol of the global minimum. Data supporting this value are frequently derived from heats of sublimation. However, some theoretical studies have already called this figure into question.[25] It is worth noting that there is an issue over how this energy window is defined:

- If derived from an experiment in which the final conformational state of molecules sublimed from two polymorphs is identical to that in the solid state, the 1-kcal/mol window relates to an intermolecular or ''lattice energy'' difference.

- If not, the molecules in the vapor may take on a common, lower energy conformation and an intramolecular contribution must be included in the equation. The 1-kcal/mol window then relates more closely to a difference between the ''total energies'' of the polymorphs.

The terms ''lattice'' and ''total energy'' will be included later in this study. Whatever definition is most appropriate, the location of all possible crystal structures in this energy window can be termed ''polymorph prediction.'' This is despite the fact that it is not currently possible to simulate the aspects of experimental crystallization that inevitably influence the crystal form produced.

Detailed descriptions of the structure prediction method used here, developed by Karfunkel and Gdanitz and implemented in the C^2 POLYMORPH computer program, have been published elsewhere.[19,29] This section will not reproduce these descriptions, but rather list the stages of the methodology, and the parameters that the user can modify in the structure prediction process.

The initial step in the approach of Karfunkel and Gdanitz is to apply a Monte Carlo (MC) search algorithm, in conjunction with simulated annealing (SA) and the Metropolis acceptance criterion, to locate possible packing arrangements of a given molecular structure. The DREIDING 2.21 force field is used and the electrostatics are based on ESP charges. The search is constrained by the symmetry operations of a chosen space group. There are three important parameters that can be set by the user at this stage of the process:

1. N_accept—the number of structures which are accepted for the system to be considered a ''melt.''
2. Heat_Factor—defines the rate of heating during the attainment of a ''melt.''
3. Cool_Factor—similarly defines the rate of cooling. This parameter is particularly important, as it affects the number of MC moves per unit temperature of SA. Reducing Cool_Factor increases the probability of locating all possible structures.

The values used for these parameters, and others governing the predictive method, are listed in Table I.

The MC/SA procedure can generate many thousands of crude structures of which a significant number will be similar. Thus, a ''clustering'' process is applied to reduce the number of structures. The important parameter for clustering is termed ''tolerance.'' The lower this value, the more similar a structure must be to the reference structure to be deemed to have the same packing arrangement. Its value would ideally cluster structures that would fall into the same minimum on the potential energy hypersurface.

TABLE I.
Important User-Defined Variables in C^2 Polymorph and Values Used.

Parameter	Value
N_accept	14
Heat_Factor	0.025
Cool_Factor	0.0015
Tolerance	0.15
RMSF	0.0001

Each crude structure which survives clustering is subjected to a minimization in which all of the degrees of freedom, including the conformation of the molecules and the unit cell parameters, are allowed to relax. The symmetry elements of the chosen space group are retained. Minimization terminates after a user-defined level of ''RMSF''; the root-mean-squared force for convergence (see Table I).

In this study, structure prediction was performed using the RHF/6-31G**-optimized CSC as a basis, in the space groups $P2_1/c$ (the space group of the known structure), C2/c, $P\bar{1}$, $P2_1$, and $P2_12_12_1$. These five space groups account for approximately 75% of the structures in the Cambridge Structural Database[27,30] and thus represent a reasonable search of likely space groups. Initial trial runs were performed at increasingly intense search criteria until a structure similar to the minimized CS (CS_min) was found. The values of user-modifiable parameters used to achieve this are listed in Table I. This level of search was then repeated in four further runs to gain some feeling for the reproducibility of the search.

The similarity of a predicted structure to the CS and the CS_min was calculated using a ''similarity'' measure described in the CERIUS[2] program manual as ''examining the partial radial distribution functions between pairs of force field atom types of the two structures being compared.''[19] The smaller the value of this similarity measure, the more similar the structures being compared. In this article, a successful polymorph run has been

classified as one in which a structure is found having a similarity measure of less than 0.1 against the CS_min.

During investigation of the gas-phase conformational maps of aspirin, an alternative low energy conformer (LC) was discovered. This molecular arrangement was optimized at the RHF/6-31G** level and used in a search for alternative CSs in the space group $P2_1/c$.

Results and Discussion

The gas-phase conformational maps were generated from the basic data using the GMT program[31]. The two different approaches (see earlier) produced maps that were qualitatively similar. The maps for approaches ''a'' and ''b'' are displayed in Figure 3a and b. Each indicates that the CSC lies within a valley of low conformational energy. However, AM1 data suggested that a planar conformer (PC, with $\tau_1 = \pm 180, \tau_2 = 0$), would be less stable than that of the CS ($\tau_1 = -81.4, \tau_2 = -5.7$), while DREIDING calculations indicate that the PC is most stable. All calculations suggested that another low energy conformer (LC) might exist. AM1 values show that the LC lies in the bottom of a valley and is approximately 3.5 kcal/mol less stable than the CS conformer. The existence of such a conformer has also been demonstrated in the work of Han and Kang.[32] For DREIDING 2.21, the LC was some 3.7 kcal/mol less stable than the CS conformer. The structure and energetic details of the three conformers just referred to are listed in Table II. It is of interest to note that the carboxylic acid generally remains within the plane of the phenyl group, supporting the previous decision not to consider this rotation in conformational mapping. However, it can also be seen (Table III) that some conformations have τ_3 greater than 20° with a maximum of 36.7°. This indicates that the carboxylic acid group was allowed some flexibility within the polymorph predictor, but it would appear that the most stable conformation is one where it is planar with the phenyl group.

Although there are concerns about calculating the relative stability of conformers using *ab initio* methods on molecules in fixed geometries,[25] this approach was used to gain a benchmark that might confirm the accuracy of AM1 results versus those obtained using DREIDING 2.21. Geometries for the CSC and the PC were derived from DREIDING 2.21, and their energies calculated using the RHF formalism at the 6-31G** level. The results were in agreement with those of the AM1 conformational maps, ranking the PC approximately 1 kcal/mol less stable than the CSC.

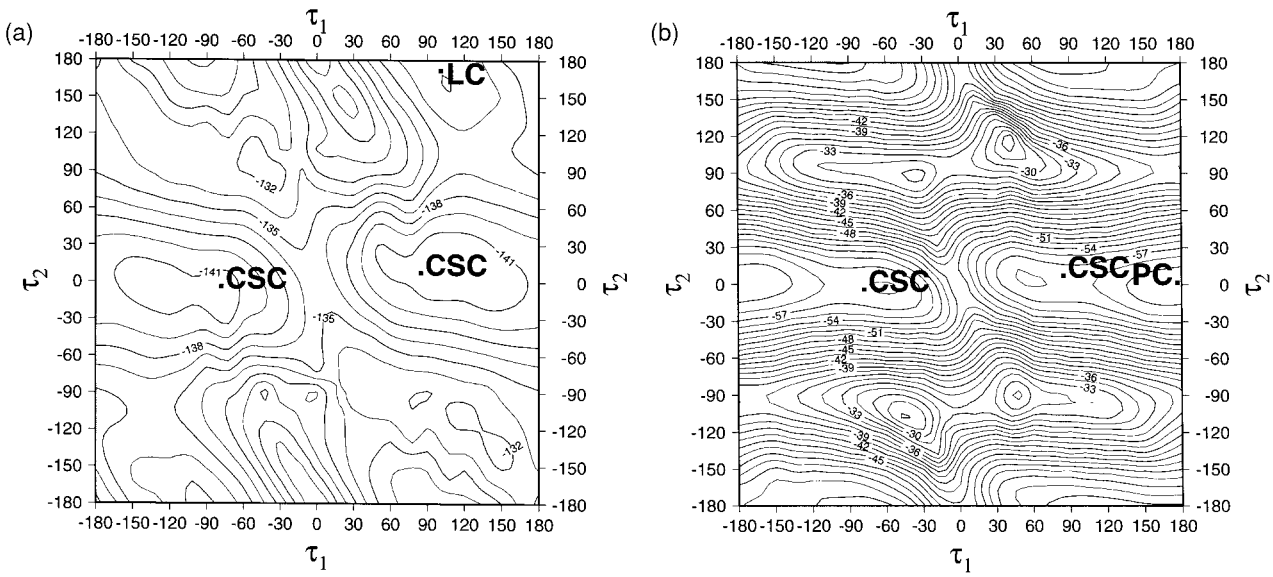

FIGURE 3. Conformational maps of τ_1 and τ_2 for aspirin generated using: (a) AM1, (b) Dreiding, and ESP charges. The contours are at intervals of 1.5 kcal / mol. The positions of the three conformers investigated in this study are indicated by the small squares.

TABLE II.
Data for Low-Energy Conformers of Aspirin.

Conformer label	τ_1	τ_2	AM1 heat of formation	Dreiding energy
CSC	±81.4	±5.7	−141.8	−57.7
LC	±97.5	±175.3	−138.3	−54.0
PC	±180.0	±0.0	−140.1	−60.8

Heats of formation and energies are given in kilocalories per mole, and the torsions, τ_2 and τ_2, in degrees.

The AM1 and DREIDING 2.21 conformational maps are consistent, suggesting that the LC could conceivably exist in a solid-state structure. However, to be observed experimentally it would need to pack into a crystalline form as or more efficiently than the CSC. To investigate the relative ease with which the LC could be packed, crystal structures were predicted in $P2_1/c$. $P2_1/c$ is one of the space groups best facilitating molecular packing. It therefore provides a good test of whether one molecular conformation packs as well as another. It is also the space group of the known aspirin crystal structure. This investigation had an additional point of interest: that is, that the valley containing the LC was shown to be separated from that of the CS by a significant energy barrier. This led to the question: Would conformations be generated outside of this valley as a consequence of the polymorph prediction process?

Polymorph prediction in $P2_1/c$ was apparently successful in an initial run, using the parameters given in Table I; that is, a structure similar to the CS_min was found. This level of predictive run was repeated in an identical manner a further four times, leading to the following observations:

- None of these subsequent runs located a structure similar to the CS_min.
- The CS_min did not represent the global total energy minimum.
- Some structures were found to have the same or very similar unit cell parameters between runs, but had different similarity measures versus the CS and CS_min, indicating that their packing arrangements were different.

TABLE III.
Data for 20 Structures with Lowest Total Energy Predicted over Five Identical Repeat Runs in $P2_1/c$.

Frame no.	Energy		Conformer			Unit cell parameters				Density	Graph set	Similarity vs.:	
	Total	Lattice	τ_1	τ_2	τ_3	a	b	c	β			CS	CS_min
CS	—	—	−81.4	−5.7	−1.2	11.43	6.59	11.40	95.68	1.401	D_2^2	0.000	0.005
CS_min	−242.9	−184.9	−103.1	2.6	3.3	11.42	6.69	11.22	95.04	1.402	D_2^2	0.005	0.000
1	−244.4	−183.4	3.3	1.2	−2.5	25.00	9.04	4.14	115.8	1.419	D_2^2	0.251	0.275
2	−244.2	−183.8	−4.1	−0.2	15.0	8.26	4.02	26.91	70.10	1.426	D_2^2	0.258	0.271
3	−244.2	−183.4	−3.7	−1.6	−2.6	9.01	23.09	4.13	84.82	1.398	D_2^2	0.250	0.237
4	−244.0	−183.9	5.6	−0.5	3.7	7.97	27.52	3.88	100.40	1.431	D_2^2	0.262	0.281
5	−243.9	−183.4	1.7	−0.5	−0.5	14.13	3.91	15.75	77.40	1.411	D_2^2	0.283	0.290
6	−243.9	−183.8	−20.0	−0.6	20.6	27.05	4.06	8.17	106.58	1.393	C_2^2	0.258	0.265
7	−243.5	−183.2	10.9	1.9	−19.3	17.32	3.90	13.67	67.01	1.407	C_2^2	0.287	0.258
8	−243.4	−182.7	−3.2	−0.4	−6.8	9.03	26.99	4.03	61.54	1.388	D_2^2	0.288	0.288
9	−243.2	−183.0	−16.2	−1.2	−14.7	13.59	3.88	16.60	93.76	1.369	C_2^2	0.271	0.251
10	−243.1	−183.2	−22.2	0.1	−22.3	3.87	27.03	8.25	89.19	1.387	D_2^2	0.272	0.268
11	−243.0	−182.4	1.8	−0.1	4.0	7.98	27.62	3.98	97.01	1.375	D_2^2	0.286	0.277
12	−243.0	−184.2	−54.5	−3.9	1.7	8.49	26.54	3.85	90.36	1.382	D_2^2	0.260	0.293
13	−242.9	−184.9	−103.1	2.6	3.3	11.42	6.69	11.22	95.04	1.402	D_2^2	0.243	0.005
14	−242.9	−184.9	−5.7	−2.3	8.1	4.57	27.55	7.04	105.20	1.400	D_2^2	0.281	0.260
15	−242.8	−182.2	−16.2	−3.6	−6.5	4.08	8.29	25.90	88.26	1.367	D_2^2	0.264	0.257
16	−242.8	−182.3	−49.2	−4.3	6.0	16.16	5.25	11.49	63.27	1.374	D_2^2	0.271	0.257
17	−242.8	−183.7	−23.0	−5.6	−1.8	9.20	24.31	4.03	77.52	1.359	D_2^2	0.278	0.279
18	−242.8	−182.4	12.2	0.7	13.9	13.35	9.32	7.10	84.95	1.360	D_2^2	0.286	0.286
19	−242.7	−182.2	48.1	8.0	−2.2	9.56	26.34	3.82	115.82	1.384	D_2^2	0.289	0.267
20	−242.7	−183.8	−5.9	−0.6	−0.8	4.08	24.06	9.02	97.23	1.364	D_2^2	0.272	0.249

Frame number designated according to total energy ranking (kcal / mol). Lattice energy defined as the energy sum of intermolecular interactions. Torsion angles are given in degrees. The unit cell parameters a, b, and c are given in angstroms units, β given in degrees. Density units are given in grams per cubic centimeter. Graph set refers to the analysis of H-bond motifs described by Etter et al.[34] Similarity measurements described in text.

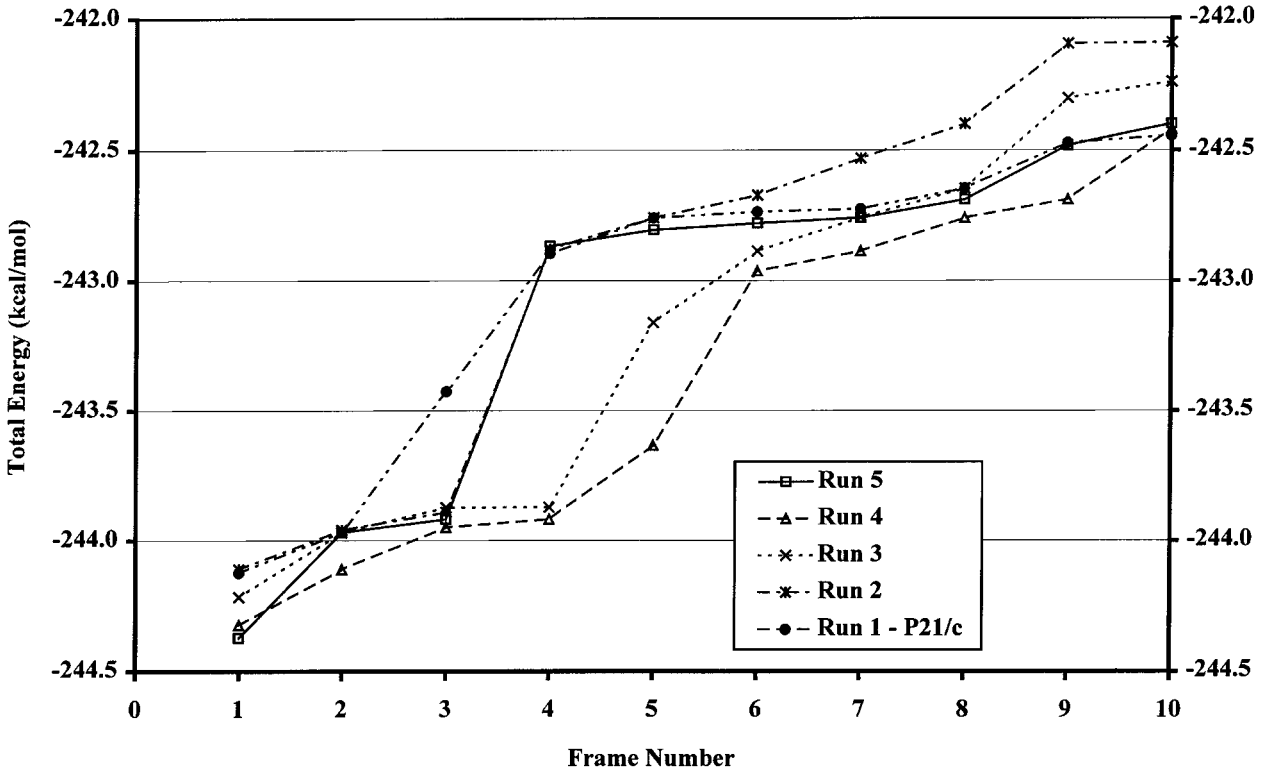

FIGURE 4. The energies of the structures located in five identical runs of C^2 Polymorph in $P2_1/c$.

Figure 4 is a graph of the energies of the ten most stable structures located in each of the five runs (C^2 POLYMORPH ranks the structures by energy and assigns a ''frame number'' accordingly, Frame 1 being the most stable structure predicted). Figure 5 contains the similarity measures for these structures versus CS_min. It is clear that the structure most similar to the CS_min (Frame 4, Run 1) is approximately 1.4 kcal/mol less stable than the predicted global minimum, with a number of other potential structures ranked as more stable. Furthermore, there are significant numbers of structures that are unique to each run. So, despite the search criteria given in Table I being sufficiently stringent for the CS_min to be found on one occasion, they were far from the level of search that might be required to exhaustively locate all possible structures in one run. Indeed, it must be concluded that, after five runs at this level, more structures remain to be found near the predicted global minimum.

It is worth noting that the CS_min is further from the global energy minimum than might have been expected. As a consequence it may be necessary to consider structures with energies perhaps 3 kcal/mol or more less stable than the predicted global minimum when looking for polymorphs that might manifest themselves experimentally. This is a much larger value that normally considered. Table III is a summary of the characteristics of the 20 lowest energy structures located over the five identical runs in $P2_1/c$. The structures in this table are relatively close in energy, when compared with those of Gavezzotti and Filippini,[21] who suggested that a structure that is 8% less stable than the predicted global minimum cannot be ruled out experimentally. However, comparison with their work is complicated by the fact that they employed a force field different from the one used here, conformations were immutable in their predictive approach, and they worked only with dimers in the centrosymmetric space groups $P2_1/c$ and $P\bar{1}$. The atomic coordinates of these structures have been saved in the format of the CSD (i.e., as *.dat files) and can be obtained from information detailed in this journal.

The energies of the ten most stable structures generated by predictive runs in four space groups other than $P2_1/c$, produced structures that were generally less stable than those observed in $P2_1/c$. These data are plotted in Figure 6. However, it is noticeable that low energy structures were pre-

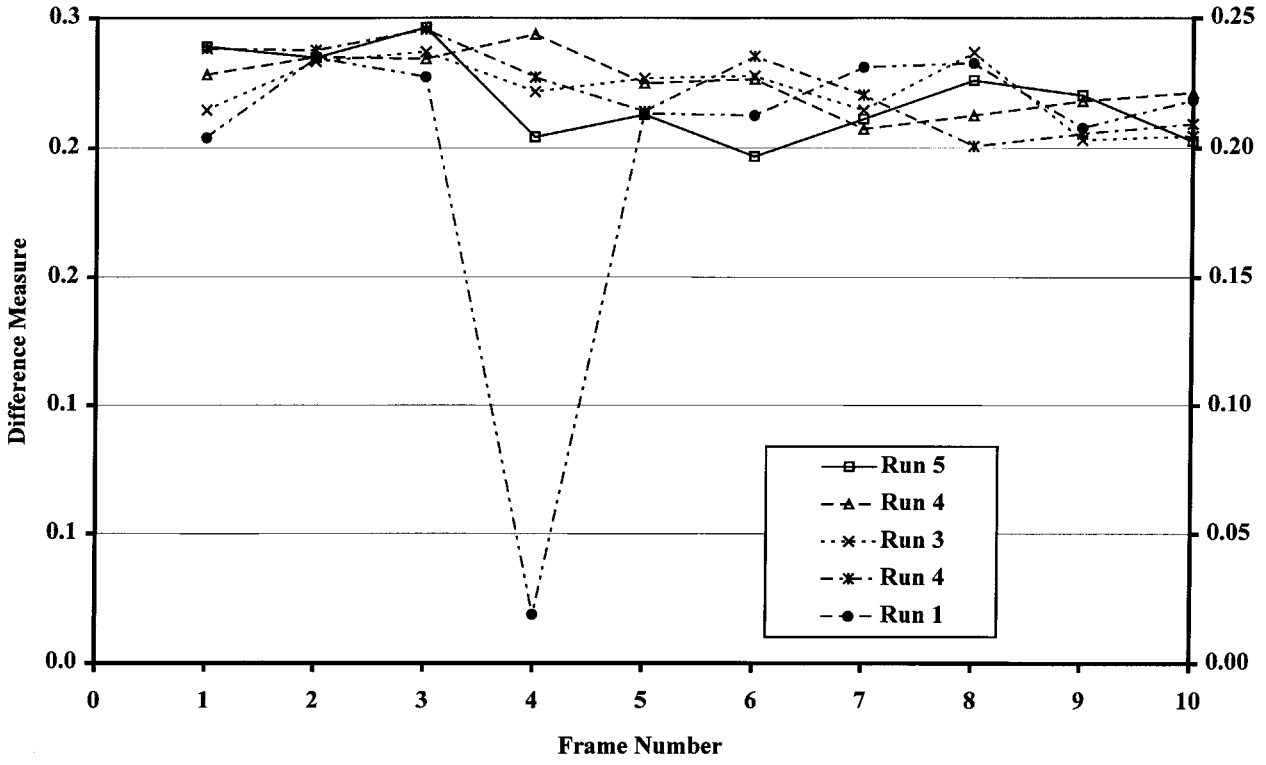

FIGURE 5. Calculated similarity measures versus CS_min, for the ten lowest energy structures in five identical runs of C^2 Polymorph in $P2_1/c$.

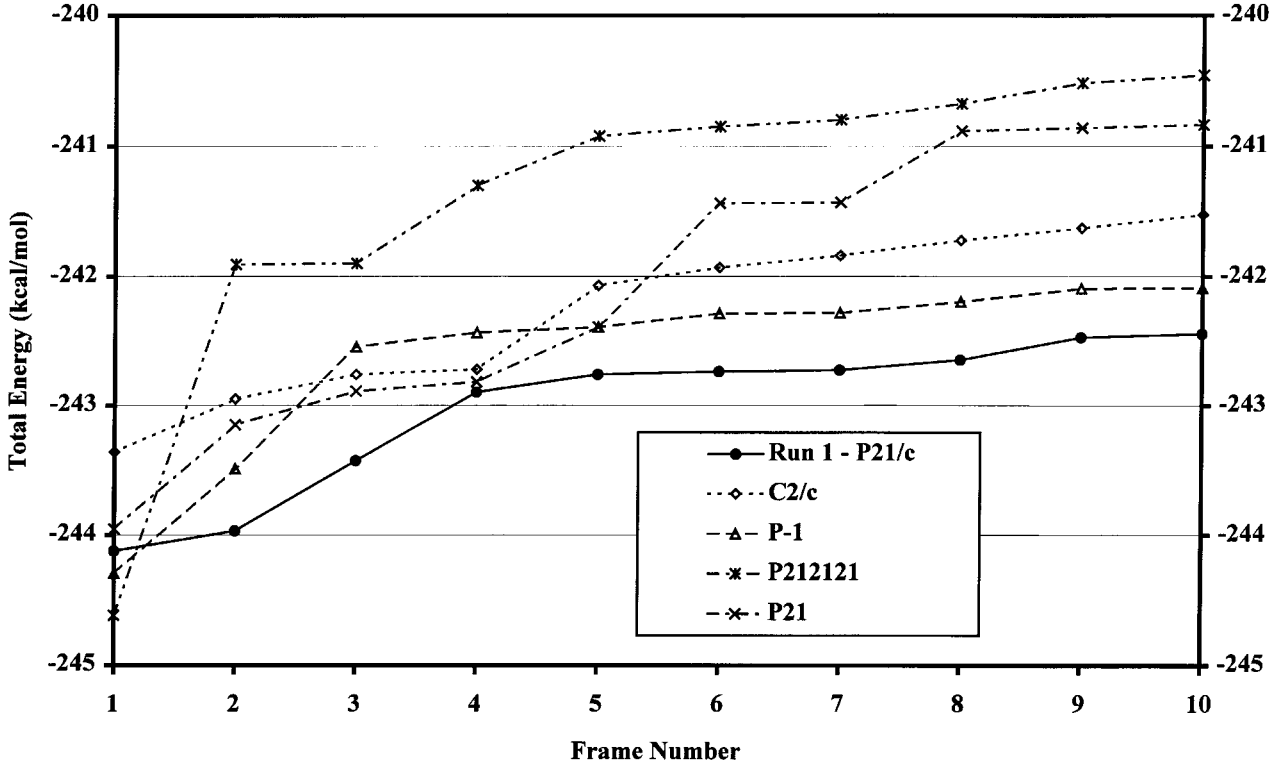

FIGURE 6. The energies of the ten lowest energy structures predicted in Run 1 in $P2_1/c$ and the other space groups: C^2/c, $P\bar{1}$, $P2_12_12_1$, and $P2_1$.

dicted in $P2_12_12_1$ and $P\bar{1}$. Given the previous comments regarding the nonexhaustive nature of the search level, many more runs would be required if firm conclusions were to be drawn regarding the relative propensity of aspirin to form polymorphs in these other space groups. It is clear, however, that the DREIDING 2.21 force field suggests the existence of a large number of unrealized crystal structures, close energetically to the known crystal structure for aspirin. Table IV groups the structures of Table III according to descriptions of their packing arrangements (PA). It is possible that these represent experimentally realizable polymorphs. If so, then the clustering process, based on the similarity measure described earlier, must be regarded as inappropriate for identifying structural types that can be generated experimentally. Of course, it remains to be proven whether any of the PA identified here (other than PA6, which includes the CS) can be generated experimentally. Unfortunately, the observations reported by previous investigators[10–12] cannot be verified because no powder x-ray diffraction data were given and therefore comparisons with this work cannot be made.

Comparison with *ab initio* and semiempirical calculations has shown that DREIDING 2.21 does not rank molecular conformers of aspirin correctly by energy. But, how does it perform with respect to intermolecular forces, as represented by lattice energies? It is recognized that, theoretically, free energies should be used especially in view of the expectedly significant entropy terms among the predicted crystal modifications. Experimental and theoretical measures of lattice energy have been used historically to rank polymorphs according to their stability[33] and may represent a more robust or practical value to rank upon than total energy used so far in this study. Indeed, this appears to be the case, when one considers column 3 in Table III. The CS_min and the most similar predicted structure to it, have a lattice energy that is 1.5 kcal/mol lower than that of the predicted total energy minimum. Only Frames 14, 12, and 4 have lattice energy within 1 kcal/mol of the

TABLE IV.
$P2_1/c$ Structures Grouped According to Packing Arrangement (PA) by Visual Inspection.

PA	Description by molecular views: Edge view	Description by molecular views: Plan view	Included frame(s)	Potential groups at surfaces
1	PC dimers lie in parallel sheets	Offset columns of molecules	1, 18	S1 + S2:— COOH S3:— O, —CH_3
2	''Herring-bone'' of PC dimers	Square array of molecules in columns	2	S1 + S2:— COOH S3:— CH_3
3	''Herring-bone'' of PC or near-CSC dimers	Offset columns of molecules	3, 4, 8, 10, 11, 12 14, 17, 19, 20	S1:— COOH S2:— COOH, phenyl
4	Cross-hatch of PC dimers	Offset columns of molecules	5	S1:— COOH, phenyl S2:— O, CH_3 S3: phenyl
5	Parallel helices of non-PC chains	Offset columns of molecules	6, 7, 9	S1:— COOH S2: phenyl
6	Cross-hatch of near-CSC dimers	Square array of molecules in columns	CS, CS_min, 13, 16,	S1:— COOH S2:— COOH, phenyl S3:— O —, CH_3
7	Mutually perpendicular columns — edges of one set seen with plan view of next set		15	S1:— COOH S2:— COOH, phenyl S3: phenyl

Potential crystal surfaces and the groups present at them are indicated by S1, etc., in order of decreasingly polar nature.

CS–min in Table III. Close examination of these structures showed that they have a similar PAs, each of which can be seen as ''herring-bone'' columns of dimers if oriented appropriately. They fall into PA 3 of Table IV. Figure 7 shows Frame 14 in this orientation. Perhaps these three frames represent an experimentally realizable form that is an alternative to the known one.

Could any of the unknown structures generated in this work be produced experimentally? What conditions might be required to make this possible? Ideally, a full theoretical model of the crystallization process would be available to help answer these questions. In the case of crystallization from solution, such a model would take into account: solvent(s) choice; temperature; concentration; driving forces for crystallization and resolvation; intermolecular forces; conformational change as molecules come together; additives or contaminants; kinetics; and entropy as well as enthalpy.

Unfortunately, as stated earlier, such a model does not exist at the moment. We are left with force-field estimates of enthalpy for potential structures like those grouped in Table IV, and our experiences of experiments in crystallization. In principle, it is possible to discover crystallization conditions that will favor the production of one polymorphic form or another.[34] However, this tends to occur by an heuristic approach. Crystallization studies have seldom if ever been exhaustive and there are few rules to apply.

It is known that different crystal structures lead to different parts of their component molecules being presented at different crystal surfaces. This means that solvents might be chosen that favor the growth of surfaces which have, for example, a certain charge distribution and, as a consequence, favor the growth of one crystal form over another. Inspection of the structures of aspirin predicted during the course of this work resulted in the information listed in the fifth column of Table IV. This lists likely surfaces (S1, S2, and S3 in order of decreasingly polar nature) and the chemical groups that would be present at them for each PA. It is not obvious that there is sufficient difference between these sets of surfaces to make solvent selection a means of generating an unknown PA. The best chance might lie in the prevalence of phenyl groups at the surface of PA5. Perhaps nonpolar solvents, and in particular aromatic ones, would favor this PA by promoting its growth or inhibiting the growth of others. However, this PA involves the chain hydrogen bonding motif, which is observed very infrequently for molecules that contain carboxylic acid groups. In addition, the solubility of aspirin is low in nonpolar solvents and there is little experimental data relating to such solutions.

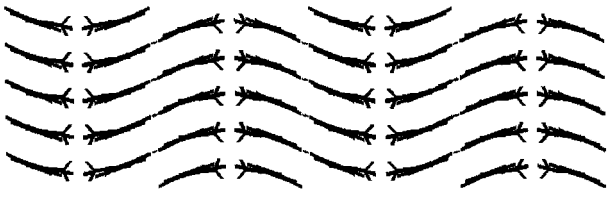

FIGURE 7. The ''herring-bone'' arrangement of Frame 14, typical of group PA3 in Table IV.

An alternative approach to generating an unknown form of aspirin might be to force a change of preferred conformation in solution. If it is assumed that the CSC is preferred in solution, it might be possible to encourage an alternative conformation; for instance, the PC, by using solvents that are themselves constricted to planar conformations. It might even be possible to force the molecules to take up a conformation stabilized by an intramolecular hydrogen bond. This possibility has been explored to some extent for analogous molecules by Etter.[26] Indeed, the PC contains a weak intramolecular hydrogen bond, as shown in Figure 9. It is feasible that the use of a polar additive, in an apolar solvent, might promote the formation of this conformer by enhancing the charge differential between the oxygen and hydrogen atoms that are associated. Ideally of course, such an additive would not be incorporated into the final crystal structure.

Even if the liquid-phase conformation of the aspirin molecule in solution can be controlled, this does not mean that it will translate into a change in conformation in the solid state. Structure prediction with the LC in $P2_1/c$ showed that the structures generated were significantly less stable than those generated with the CSC. This may be because DREIDING 2.21 strongly disfavors the LC in the gas phase and it should be recalled that this is at odds with the AM1 and *ab initio* conclusions. The results of prediction with the LC are shown in Figure 8, where the total energies of the ten most stable structures predicted with the LC are compared with those of Run 1 with the CSC. Because the gas-phase energy of the LC is approximately 3 kcal/mol higher than the CSC, Figure 8 demonstrates that the lattice energies of structures created from it must be ca. 45 kcal/mol more positive. It can concluded that the experimental

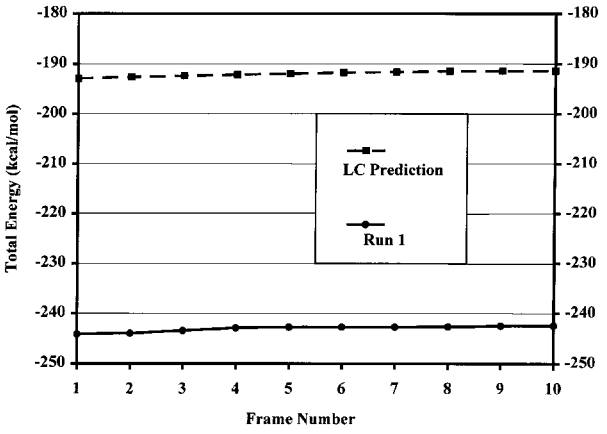

FIGURE 8. The energies of the ten most stable structures predicted in $P2_1/c$, using the LC, compared with those predicted in Run 1.

realization of polymorphs based on the LC is, energetically, highly unlikely. Analysis of the ultimate conformations adopted in the crystal structures predicted with the LC indicated that τ_1 and τ_2 had remained close to the values of the LC itself; see Table V. This confirms that, according to DREIDING 2.21, there is a significant energy barrier to conformational change between the region of the energy map occupied by the LC and that occupied by the CSC and PC. DREIDING 2.21 indicates that this energy barrier is approximately 20 kcal/mol in height. It is worth noting that AM1 calculations show this barrier to be much smaller, ca. 4 kcal/mol, suggesting that it may be less significant in reality than it appears to DREIDING 2.21. However, the importance of this observation lies in the fact that the prediction process implemented in C^2 POLYMORPH is not capable of surmounting this energy barrier. Although this observation is specific to the torsional map of aspirin, it serves to exemplify a need to identify likely conformers for packing, in advance of any attempt to predict all potential polymorphic forms by this process.

TABLE V.
Torsion Angles, τ_1 and τ_2, for Molecules in Crystal Generated in $P2_1/c$ Using LC.

Frame number	$\tau_1(\pm)$	$\tau_2(\pm)$
1	94.1	178.4
2	94.2	177.6
3	96.8	176.7
4	84.8	177.1
5	52.7	173.2
6	97.1	177.4
7	92.8	178.6
8	100.5	173.9
9	93.5	178.1
10	46.4	173.3

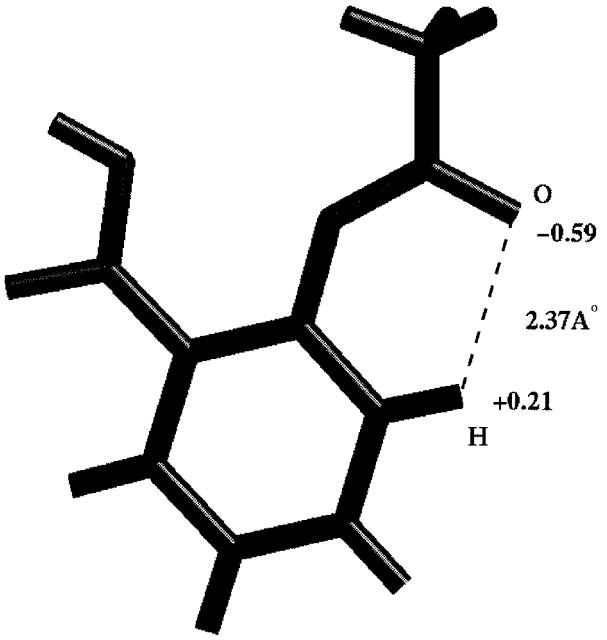

FIGURE 9. A weak intramolecular hydrogen bond (represented by a dashed line, length given in angstrom units), which might aid stability of the PC in appropriate solvents. The charges on the oxygen and hydrogen atoms are given as fractions of the charge on an electron.

Conclusions

- The search for potential polymorphic structures in $P2_1/c$ was incomplete after five identical and relatively intense runs of C^2 POLYMORPH. Although tighter criteria were used than the program defaults, even tighter critera would be required if the results of individual runs were to be reproducible.
- DREIDING 2.21 has significant deficiencies in its description of the conformation of aspirin, as well as in its description of hydrogen bonding and other important interactions.
- When using this predictive methodology to search for potential polymorphs, it is necessary to consider a wider total energy window above the predicted global minimum than historical data might suggest (e.g., 3 kcal/mol rather than 1 kcal/mol). This may, at least in part, be a consequence of the deficiencies of DREIDING 2.21.

- A suggested approach to the search for potential structures that are experimentally realizable is to: group predicted structures by their packing arrangements; consider the surfaces these arrangements might present; and design a crystallization process accordingly. It may also be possible to consider the molecular conformers of which potential structures are composed and use crystallization conditions that favor these conformers.
- In the case of aspirin, the use of solvent systems with phenyl groups might lead to the production of alternative forms. However, potential structures created from a conformer close to the global minimum conformation (the LC) did not pack well, indicating that the experimental production of structures based upon it is unlikely.
- It is necessary to rigorously explore potential conformers of a particular molecule prior to structure prediction. Otherwise, there is a significant chance that the vast majority of potential polymorphs will be missed by the prediction process because energy barriers may not be surmounted between conformations.

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